IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

MAILLAND — Atty. Ref.: 622-89; Confirmation No. 7507

Appl. No. 10/559,794 — TC/A.U. 1655

Filed: December 8, 2005 — Examiner: Anderson, H.L.

For: NAIL RESTRUCTURING COMPOSITIONS FOR TOPICAL APPLICATION

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

I, Federico Mailland, hereby declare and state that:

1. I am the named inventor in the present application.

2. I graduated as Medical Doctor in 1975. I was awarded a postgraduate diploma in Pharmacology in 1977 and a postgraduate diploma in Science of Nutrition in 1980. Since graduation, I have worked in R&D departments of different pharmaceutical companies and have focused on the development of several pharmaceutical products. As Medical Director of a pharmaceutical company since 1977, as Director, Research and Development since 1982, and as Scientific Director, since 1991, I was responsible for development of proprietary medicinal products (NCEs, new technologies) in SNC (Parkinson's; Alzheimer's; migraine) and in immunology. I also developed products in the cardiovascular, gynaecological and respiratory areas. I directed preclinical development and phase I-IV clinical trials in European Countries. I implemented GCP

and QA audits. I built up a department of International Regulatory Affairs. Under my responsibility, several patent applications were filed (most of which were granted) in the US, Germany, France, Italy, Spain; in Eastern European Countries, in China and in Latin America. In Italy, I was involved in the creation of the first and the most important generic Company in the Italian market, namely Dorom srl. I built up a Unit of Pharmacovigilance with a centralized database, operating expedited reporting, follow up and safety update reports for the Companies of the group and for licensees.

3. During the period since 2000 onwards, my activity has been mainly directed to the development of new original technologies for drug delivery to nails and to skin or scalp. I applied as inventor of 5 International Patents of new technologies for products of interest in dermatology. Two of them are already worldwide granted and three others are pending. I participated with presentation of communications in International Conferences of the American Academy of Dermatology, International Society for Bioengineering and the Skin, European Academy of Dermatology and Venereology, European Society for Dermatological Research, World Congress of Dermatology, International Academy of Cosmetic Dermatology, and in Conferences of the National Societies of Dermatology in Italy, France and Germany.

4. I am Scientific Editor of 4 books and 2 issue supplements of Scientific Journals; Author of 86 peer-reviewed papers and over 100 abstracts from National and International Conferences; Inventor of 7 internationally granted patents.

5. A copy of my CV is attached.

6. I have studied the above application, the outstanding Official Action and the cited art, particularly the PDR for Herbal Medicines (1998) and Koniger et al. (WO 94/25041 - Derwent Abstract plus Machine Translation thereof).

7. In the outstanding Official Action, it is asserted that:

> "Accordingly, the topical use of *Equisetum* (including in the form of an extract thereof) for treating brittle nails (whatever the underlying pathology) -including brittle nails widespread and commonly caused by onychoschizia or brittle nails resulting from and/or commonly associated with onychomycosis, would clearly have been obvious based upon the beneficial teachings provided by the primary references cited above, for the reasons set forth in the previous Office action."

8. I do not agree with the above assertion for the following reasons.

9. The invention as claimed is directed to a method of treating onychoschizia by administering to a patient in need thereof a topical composition comprising (a) at least one herb extract from the genus *Equisetum*, and (b) at least one film forming agent.

10. My review of the cited references reveals that none of them suggests the use of an extract from *Equisetum* for the treatment of onychoschizia and, moreover, none of them suggests that a topical composition comprising such extract would be useful in treating onychoschizia.

11. As described in the present specification (pages 3 and 4), and confirmed by Enclosure 1 (submitted with the prior response and further copy attached hereto), onychoschizia is not a generic condition of nail brittleness, but rather a specific and well-characterized pathology of the nails, wherein the distal portion of the nail splits horizontally.

12. While PDR for Herbal Medicine (PDR) reports that *Equisetum* may be used for the treatment of "brittle finger nails and loss of hair", the efficacy of such use "is not proven" and moreover there is no suggestion in PDR to apply *Equisetum* topically onto nails.

13. Although Koniger discloses the use of *Equisetum* extracts in the treatment of onychomicosis, there is no mention in this reference of treatment of brittle and splitting nails.

14. Onychomicosis and onychoschizia are different and unrelated conditions, and require two completely different treatments. In particular, as described in Enclosure 2 (attached to the prior response and further copy attached hereto), onychomicosis is a fungal infection of the nails, caused by specific microorganisms and its treatment requires the use of antimycotic agents. In this pathology, the nail structure is damaged by the fungi that grow inside the nail and render the nail more fragile. Onychomicosis is never a cause of onychoschizia, but it is frequently a cause of onycholysis, i.e., a detachment of the full nail plate from the nail bed.

15. Example 10 of the present application describes the results of a study of subjects previously affected by onychomicosis, from which it can be seen that, after treatment with the claimed composition, no effect was seen in these subjects regarding onycholysis, whereas a definite improvement was recorded with onychoschizia (a significant improvement ($p<0.001$) was observed compared to untreated nails).

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the

like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Federico Mailland

July 14th, 2009
Date

Attachments: Enclosures 1 and 2; CV

CURRICULUM VITAE

Federico Mailland, MD

DATE OF BIRTH: August 2nd, 1949

PLACE OF BIRTH: Milan, Italy

STATUS: Married, 3 children

ACADEMIC DEGREES: 1975: MD, University of Milan

EDUCATION AND TRAINING:

Institution	*Title*	*Year*
University of Milan	M.D.	1975
University of Milan	Postgraduate diploma Pharmacology	1974
University of Milan	Postgraduate diploma Science of Nutrition	1978

PROFESSIONAL ACTIVITY AND EMPLOYMENTS:

1975- onwards (Milano, Italy)
Professional activity as General Practitioner

1974-1981 Pierrel S.p.A. (Pharmaceutical Company) (Milano, Italy)
1974-1977 Clinical Research Associate.
1977-1981 Medical Director.
He contributed to the development of antibiotics and food supplements, by managing phase III clinical studies. He directed phase IV clinical studies on antibiotics and local anaesthetic agents.

1981-2000 Poli Industria Chimica (Pharmaceutical Company) (Milano, Italy)
1981-1982 Assistant to the General Manager
1982-1991 Director, Research and Development
1991-2000 Scientific Director
Responsible of development of proprietary medicinal products (NCEs, new technologies) in SNC (Parkinson's; Alzheimer's; migraine) and in immunology. He developed also products in cardiovascular, gynaecological and respiratory areas.
He directed preclinical development and phase I-IV clinical trials in European Countries. He implemented GCP and QA audits.
He participated in the launch of products of the Company, mainly in Italy, in Switzerland, in Germany and in China, by phase IV clinical trials, Congress presentations, publications, training of sales force.

He built up a department of International Regulatory Affairs. Under his responsibility several applications were filed (most of them granted) in Italy, Germany, France, Spain; in Eastern European Countries and in China; in Latin America.
He contributed to create in Italy the first and the most important generic Company in the Italian market, namely Dorom srl.
He built up an Unit of Pharmacovigilance with a centralized database, operating expedite reporting, follow up and safety update reports for the Companies of the group and for licensees.

2000- onwards Polichem S.A., (Pharmaceutical Company) (Lugano, Switzerland)
Since April 2000 he contributed to build up the new pharmaceutical Company Polichem S.A., company of Poli group in Lugano, Switzerland, where the headquarter for the International activities of Poli was transferred. He is working in Polichem as Scientific Director, with the responsibility of managing R&D activities, including galenic development, screening, nonclinical and clinical development. Pharmacovigilance and world-wide Regulatory Affairs are also part of his responsibility. He is the Qualified Person for Pharmacovigilance of the Companies belonging to Poli group.
Under his responsibility, the activities of the Company in this period were extended to the US, where under license of Polichem or under co-development agreements four NDAs were already granted by the FDA for medicinal products.
He is responsible of development of proprietary technologies, mainly directed to topical application of medicinal products and medical devices (gynaecology and dermatology). Under his responsibility the Company started in 2007 a new line of chemical synthesis and screening of new chemical agents in the field of antimycotics, endowed with an innovative mechanism of action.

EXPERIENCE IN DERMATOLOGY:

During the period since 2000 onwards, his activity was mainly directed to the development of new original technologies for drug delivery to nails and to skin or scalp. He applied as Inventor of 5 International Patents of new technologies for products of interest in dermatology, two of them already worldwide granted, three other pending. He participated with presentation of 20 oral communications or posters in International Conferences of the American Academy of Dermatology, International Society for Bioengineering and the Skin, European Academy of Dermatology and Venereology, European Society for Dermatological Research, World Congress of Dermatology, International Academy of Cosmetic Dermatology, and in Conferences of the National Societies of Dermatology in Italy, France and Germany. He is Author of 2 peer-reviewed original papers, other papers are pending.

SCIENTIFIC ACTIVITIES:

- Scientific Editor of 4 books and 2 issue supplements of Scientific Journals

- Author of 86 peer-reviewed papers and over 100 abstracts from National and International Conferences
- Inventor of 7 internationally granted patents

FELLOWSHIPS OF PROFESSIONAL SOCIETIES:

- ESDR, European Society for Dermatological Research
- AAD, American Academy of Dermatology
- IACD, International Academy od Cosmetic Dermatology
- AFTI, Society of Pharmaceuticals from Ticino (Switzerland)
- SSFA, Italian Society of Applied Pharmacological Sciences

TOPICS OF INTEREST AND FIELDS OF RESEARCH:

- Dermatophytoses and onychomycosis
- Nail psoriasis
- Seborrheic dermatitis
- Technology for drug delivery to nails
- Film forming technology for application to skin and scalp
- Microbiology
- New antimycotic agents

Lugano, July 9th, 2008

Federico Mailland - References

Books

1.
GENAZZANI A.R., VOLPE A. and **MAILLAND F.** (eds)
Dihydroergocristine: Clinical Neuroendocrinology
Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988

2.
GENAZZANI A.R., VOLPE A., FACCHINETTI F. and **MAILLAND F.** (eds)
Dihydroergocriptine: Gynecological Endocrinology
Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1990

3.
GENAZZANI A.R., FACCHINETTI F. and **MAILLAND F.** (eds)
Sindrome premestruale e diidroergocriptina: correlazioni neuroendocrine e strategie terapeutiche
Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1990

4.
GENAZZANI A.R., VOLPE A., and **MAILLAND F.** (eds)
Diidroergocriptina e iperprolattinemie
Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1990

Issues

1.
MAILLAND F. (ed)
Dihydroergocristin – Aktueller Stand von Forschung und Entwicklung
Arzneim.Forsch. (1992) 42 (11) 43 pp.

2.
MAILLAND F. (ed)
Pidotimod – A new Biological Response Modifier
Arzneim.Forsch. (1994) 44 (II): 131 pp.

Theses

1.
MAILLAND F.
Vie del dolore e loro controllo farmacologico
Tesi di Laurea in Medicina e Chirurgia - Università di Milano - Anno Accademico 1973 - 1974

2.
MAILLAND F.
Studio preliminare comparativo su di un nuovo composto antiinfiammatorio non steroideo
Tesi di Specializzazione in Farmacologia Applicata all'Industria - Università di Milano - Anno Accademico 1976 - 1977

3.
MAILLAND F.
Alimentazione del prematuro con latti formulati. Contributo personale.
Tesi di specializzazione in Scienza dell'Alimentazione - Università di Milano - Anno Accademico 1979 - 1980

Patents

1.
POLI S., **MAILLAND F.**, COPPI G. (1991)
ALPHA-DIHYDROERGOCRYPTINE PHARMACEUTICAL PREPARATIONS WITH NEUROPROTECTIVE ACTIVITY
Granted in EU, Canada

2.
POLI S., **MAILLAND F.**, COPPI G. (1991)
NEURO-PROTECTIVE AGENTS PREVENTING NERVE DAMAGE - CONTAIN ERGOT DERIVATIVES
Granted in Italy

3.
POLI S., **MAILLAND F.**, COPPI G., SIGNORELLI (1991)
L-THIAZOLIDINE-4-CARBOXYLIC ACID DERIVATIVE, PROCESSES FOR THE PREPARATION THEREOF AND THE USE THEREOF IN THERAPY
Granted in Italy

4.
POLI S., **MAILLAND F.**, MORO L. (1996)
PHARMACEUTICAL COMPOSITIONS FOR TRANSMUCOSAL DELIVERY OF PEPTIDES
Granted in US, EU, Canada

5.
MAILLAND F. (2000)
METHODS FOR MAKING SUSTAINED RELEASE PH.COMP. OF ERGOT ALKALOIDS HAVING IMPROVED BIOAVAILABILITY AND COMPOSITIONS THEREOF
Granted in EU

6.
MAILLAND F. (2001)
NAIL VARNISH COMPOSITION
Granted in US, EU, China, Russia

7.
MAILLAND F. (2005)
NAIL RESTRUCTURING COMPOSITIONS FOR TOPICAL APPLICATION
Granted in EU

Original Papers

1. (p)
QUATTRINI M., BRIGNOLI A., DEZZA O., **MAILLAND F.**, BATTAGLIA A.
Prova clinica comparativa in ortopedia con due farmaci antiinfiammatori non steroidei
Atti Accad. Med. Lomb. (1977) 32:

2. (p)
CACCIARI C., MALAGUTI P., ZINCATI G., **MAILLAND F.**
Considerazioni sull'uso della pifarnina nel trattamento della patologia peptica
La Clinica (1979) 34:

3. (p)
MARITANO M., DEZZA O., PAGNI R., **MAILLAND F.**, BATTAGLIA A.
Comportamento di alcuni parametri umorali prima e dopo dieta arricchita con G-1OOO
(5O osservazioni su atleti P.O. dello sci di fondo)
Med. Sport. (1979) 32: 425-436

4. (p)
GATTI E., **MAILLAND F.**
Comportamento nutrizionale della gestante (Ruolo attuale dell'ostetrico in riferimento alle abitudini dietetiche in gravidanza)
Min. Gin. (1981) 33: 447-454

5. (p)
RAMAIOLI F., PAGANI I., MARRA M., **MAILLAND F.**, MAGNANI P.
Sperimentazione clinica comparativa con Bupivacaina allo O,75% e O,5O% in chirurgia ortopedico-traumatologica
Min. Anest. (1981) 47: 271-28O

6. (p)
GHINELLI C., BASSANI F., DEL ROSSI C., VITALI M., PANTANO S., **MAILLAND F.**
Associazione della TPN e della EN nella terapia intensiva del grave ustionato pediatrico
Min. Diet. e Gastr. (1981) 27: 277-278

7. (p)
GHINELLI C., BASSANI F., DEL ROSSI C., VITALI M., **MAILLAND F.**
Terapia intensiva della enterocolite necrotizzante (NEC)
Min. Diet. e Gastr. (1981) 27: 365-366

8. (p)
FERRARI C., ROMUSSI M., BENCO R., RAMPINI P. **MAILLAND F.**
Effect of dihydroergocristine administration on serum prolactin and GH levels in normal, hyperprolactinemic and acromegalic subjects
J. Endocrinol. Invest. (1982) 5: 62
Proceedings of the XIX National Congress of the Italian Society of Endocrinology - Genova, Fiera del Mare, May 11 - 14, 1982

9. (p)
ZUNIN C., ASTORI L., GANDINI D., **MAILLAND F.**, MILANI M.
La nutrizione del bambino di peso neonatale molto basso (15OO g). Esperienza con una formula per prematuri.
Ped. Med. Chir. (Med. Surg. Ped.) (1983) 5: 333-34O

10. (p)
SEGA R., **MAILLAND F.**, DAMIANI E., GROOTHOLD G., LIBRETTI A.
Indenolol in hypertension
Clin. Pharmacol. Ther. (1983) 33: 289-293

11. (p)
SEGA R., **MAILLAND F.**, DAMIANI E., COLOMBO F., GROOTHOLD G., LIBRETTI A.
Further evaluation of antihypertensive activity of indenolol
Curr. Ther. Res. (1983) 33: 312-316

12. (p)
MAILLAND F., FELICI E., PIATTI M.
Dihydroergocristine surveillance in chronic cerebrovascular disease
Curr. Ther. Res. (1983) 33: 997-1OO3

13. (p)
FERRARI C., ROMUSSI M., BENCO R., RAMPINI P., **MAILLAND F.**

Effect of dihydroergocristine administration on serum prolactin and growth hormone levels in normal, hyperprolactinemic, and acromegalics subjects: further evidence for pituitary dopamine deficiency in these conditions
Acta Endocrin. (1983) 103: 1-6

14. (p)
VENITZ J., LUECKER P.W., ALBRECHT H., **MAILLAND F.**
Measuring the inhibition of TRH stimulated prolactin by dihydroergocristine (DEC) in man: an indirect assessment of bioavailability
Meth and Find Exptl Clin Pharmacol (1984) 6: 645-647

15. (p)
FERRARI C., RAMPINI P., PARACCHI A., BOGHEN M., **MAILLAND F.**
Effect of dihydroergokryptine administration on serum prolactin and growth hormone levels in normal, hyperprolactinemic and acromegalic subjects: evidence for potent and long-lasting pituitary dopamine receptor stimulation
Eur. J. Clin. Pharmacol. (1985) 27: 707-711

16. (p)
MALACCO E., MILANESI A., MERONI R., DAGANI R., **MAILLAND F.**
Effetti dell'indenololo sulla omeostasi glucidica in pazienti ipertesi
Basi Raz. Ter. (1985) 15: 33-34

17. (p)
LAZZARONI M., PARENTE F., **MAILLAND F.**, BIANCHI PORRO G.
Timepidium bromide as premedication before duodenoscopy
Ther. Res. (1985) 37: 288-283

18. (p)
MALACCO E., **MAILLAND F.**, BEVILACQUA M., BOSISIO E., MERONI R.
Long-term hemodynamic effects of indenolol in hypertension at rest and during isometric exercise
Curr. Ther. Res. (1985) 37: 537-544

19. (p)
SEGA R., **MAILLAND F.**, COLOMBO F., GROOTHOLD G., PANTAROTTO C., GUENZATI G., LIBRETTI A.
Indenolol pharmacokinetics and pharmacodynamics after single and repeated once a day dosis
J. Clin. Pharmacol. (1985) 25: 337-342

20. (p)
SCARZELLA L., SCARZELLA R., **MAILLAND F.**, BERGAMASCO B.
Amineptine in the management of the depressive syndroms
Prog. Neuro-Psychopharmacol. e Biol. Psychiat. (1985) 9: 429-439

21. (p)
POLI M., COCCHI D., **MAILLAND F.**, MASU A.M., LANDI G., CRAVERI A.A., MUELLER E.E.
Prolactin lowering effect of dihydroergokryptine in rat and in man
J. Endocrinol. Invest. (1986) 9: 31-36

22. (p)
MALACCO E., **MAILLAND F.**, BOSISIO E., MERONI R., DAGANI R., RENESTO E., BEVILACQUA M.
Acute and long-term hemodynamic effects of propranolol and indenolol in hypertension
Eur. J. Clin. Pharmacol. (1986) 30: 157-160

23. (p)
MAILLAND F., GROOTHOLD G., POLI A., PANTAROTTO C.
Indenolol kinetics vs pharmacodynamics in hypertension
Meth. and Find. Exptl. Clin. Pharmacol. (1986) 8(9): 567-574

24. (p)
MAILLAND F., ZOTTINO G.
Therapeutische Effektivität und Sicherheit von Dihydroergocristin
Fortschr. Med. (1986) 104: 239-242

25. (p)
MARTUCCI N., MANNA V., **MAILLAND F.**
EEG-Pharmacological and Neuropsychological Study of Dihydroergocristine Mesylate in Patients with Chronic Cerebrovascular Disease
Advances in Therapy (1986) 3: 210-223

26. (p)
VOLPE A., BARALDI R., STORCHI A.R., PAMPARANA F., **MAILLAND F.**, GENAZZANI A.R.
Dihydroergocristine in the treatment of borderline hyperprolactinemia

In: A.R. Genazzani, A. Volpe and F. Facchinetti (eds.) - Gynecological Endocrinology, pp 259-265. (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1986)

27. (p)
CORRADI L., GROOTHOLD G., VENCO A., **MAILLAND F.**, NEGRI F., GRANDI A., BARZIZZA F., FINARDI G.
Effect of indenolol treatment upon beta-adrenergic receptors of polymorphonucleates in essential hypertension
J. Hypertension (1986) 4 (suppl. 6): 137-140

28. (p)
DI PERRI R., **MAILLAND F.**, BRAMANTI P.
The effects of amineptine on the mood and nocturnal sleep of depressed patients
Prog. Neuro-Psychopharmacol. & Biol. Psychiat. (1986) 11: 65-70

29. (p)
MAILLAND F.
Gli alcaloidi idrogenati dell'ergot: razionale per l'impiego nel trattamento del morbo di Parkinson.
In: G. Nappi e T. Caraceni (ed.). Atti del II Corso di Aggiornamento sul Morbo di Parkinson e Malattie Extrapiramidali pp. 269-279 (Pavia: Edizioni Mediche Italiane) 1987

30. (p)
MAILLAND F., FAINI D., TURBA C.
Proprietà farmacologiche dell'indenololo
Atti del Simposio Satellite all' 87° Congresso Nazionale della Società Italiana di Medicina Interna: Ruolo della β_2-stimolazione vascolare nel controllo dell'ipertensione arteriosa- Roma, 11 ottobre 1986

31. (p)
MALACCO E., GNEMMI A.E., MAGENTA M., **MAILLAND F.**
Effetti long-term dell'indenololo sull'anatomia e funzionalità del ventricolo sinistro nell'ipertensione arteriosa essenziale
Acta Medica Mediterranea (1987) 3: 233-240

32. (p)
MALACCO E., GNEMMI A.E., MAGENTA M., **MAILLAND F.**
Emodinamica del paziente iperteso ed effetti della stimolazione β_2-vascolare
Acta Medica Mediterranea (1987) 3: 307-312

33. (p)
FAGLIA G., CONTI A., MURATORI M., TOGNI E., TRAVAGLINI P., ZANOTTI A., **MAILLAND F.**
Dihydroergocriptine in Management of Microprolactinomas
J. Clin. Endocrinol. Metab. (1987) 65: 779-784

34. (p)
MAILLAND F., STORCHI A.R., ZANOTTI A., VOLPE A.
Hydrogenated ergot alkaloids in the management of hyperprolactinemia
In: A.R. Genazzani, V. Montemagno, C. Nappi and F. Petraglia (eds): The Brain and Female Reproductive Function, pp 579-585. (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

35. (p)
MALACCO E., GNEMMI A.E., BEVILACQUA M., MAGENTA M., GROOTHOLD G., **MAILLAND F.**
Effects of cardioselectivity and β_2-stimulation on serum potassium regulation during isometric exercise in hypertensive patients treated with betablockers
J. Hypertension (1987) 5 (suppl. 5): 185-187

36. (p)
COLOMBO F., SEGA R., **MAILLAND F.**, RIGO R., PALVARINI L., LIBRETTI A.
Beta-blockade antagonism of tyramine-induced rise in blood pressure
Eur. J. Clin. Pharmacol. (1988) 34: 263-266

37. (p)
ANNONI F., POLI A., ZOTTINO G., **MAILLAND F.**
Studio epidemiologico e di farmacovigilanza su 1353 pazienti arteriopatici periferici trattati con ciclonicato
Giornale Italiano di Ricerche Cliniche e Terapeutiche (1987) 8: 145-152

38. (p)
MAILLAND F., POLI A., ZOTTINO G.
Drug surveillance of dihydroergocristine in long-term use
Curr. Ther. Res. (1987) 42: 857-861

39. (p)

MAILLAND F., POLI A., AMOROSI G., LEVI MINZI A., ZOTTINO G.
Studio di farmacovigilanza con amineptina nella depressione
Quaderni Italiani di Psichiatria (1988) Numero speciale: 29-35

40. (p)
CANONICO P.L., **MAILLAND F.**, SCAPAGNINI U.
Dihydroergocristine-mediated inhibition of prolactin release: involvement of multiple intracellular signals
In: A.R. Genazzani, A. Volpe and F. Mailland (eds): Dihydroergocristine: Clinical Neuroendocrinology, pp 1-14 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

41. (p)
VOLPE A., ZANOTTI A., STORCHI A.R., **MAILLAND F.**
Dihydroergocristine in the management of hyperprolactinemia
In: A.R. Genazzani, A. Volpe and F. Mailland (eds): Dihydroergocristine: Clinical Neuroendocrinology, pp. 15-22 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

42. (p)
LUECKER P.W., WETZELSBERGER N., VENITZ J., ALBRECHT H., **MAILLAND F.**
Relative bioavailability of a new dihydroergocristine (DHC) formulation in man: an indirect assessment of bioavailability
In: A.R. Genazzani, A. Volpe and F. Mailland (eds): Dihydroergocristine: Clinical Neuroendocrinology, pp. 38-46 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

43. (p)
DE ALOYSIO D., ROMUSSI A., **MAILLAND F.**, BOTTIGLIONI F., ZANOTTI A.
Dihydroergocristine in stopping lactation: double blind study vs bromocriptine
In: A.R. Genazzani, A. Volpe and F. Mailland (eds): Dihydroergocristine: Clinical Neuroendocrinology, pp. 61-67 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

44. (p)
STORCHI A.R., VOLPE A., ZANOTTI A., **MAILLAND F.**,
Treatment with dihydroergocristine in the inhibition of lactation
In: A.R. Genazzani, A. Volpe and F. Mailland (eds): Dihydroergocristine: Clinical Neuroendocrinology, pp. 77-82 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

45. (p)
MELIS G.B., CAGNACCI A., PAOLETTI A.M., GAMBACCIANI M., SOLDANI R., **MAILLAND F.**, FIORETTI P.
Effect of dihydroergocristine on LH pulsatile release and hot flushes in postmenopausal women
In: A.R. Genazzani, A. Volpe and F. Mailland (eds): Dihydroergocristine: Clinical Neuroendocrinology, pp. 83-90 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1988)

46. (p)
MALACCO E., MAGENTA M., RENESTO E., SARTINI C., **MAILLAND F.**, GROOTHOLD G.
Long-term treatment of hypertension - our experience with indenolol
Curr. Ther. Res. (1988) 44: 378-384

47. (p)
CANONICO P.L., **MAILLAND F.**, SCAPAGNINI U.
Diidroergocriptina e recettori dopaminergici a livello ipofisario e striatale
A. Agnoli e L. Battistin (ed.): Atti XIV Riunione LIMPE: "Morbo di Parkinson e Demenze: metodologie diagnostiche" Alba (Cuneo) 22 - 24 ottobre, 1987 (Pubblicazione Guanella, Roma 1988)

48. (p)
MAILLAND F.
Pharmacology of dihydroergokryptine and its role in the management of Parkinson's disease
In: G. Nappi and T. Caraceni (eds.): Parkinsonism: Diagnosis and Treatment, pp 173-181 (Laurel House Publishing Company, Inc., 1989)

49. (p)
CANONICO P.L., SORTINO M.A., **MAILLAND F.**
Diidroergocriptina e recettori dopaminergici ipofisari
Giornale di Neuropsicofarmacologia (1989) 4: 16-21

50. (p)
MARTUCCI N., FABBRINI G., LEVI MINZI A., PEDEVILLA M., **MAILLAND F.**, AGNOLI A.
La diidroergocriptina nella terapia del Morbo di Parkinson: studio clinico in doppio cieco vs bromocriptina
A. Agnoli e L. Battistin (eds.): Atti XV Riunione L.I.M.P.E. - Pisa, 27 - 29 ottobre 1988 (Pubblicazione Guanella, Roma, 1989)

51. (p)

AMBROSIONI E., BIRKENHAEGER W., DE LEEUW P.W., DAL PALU' C., DEMANET J.C., GROOTHOLD G., LIBRETTI A., **MAILLAND F.**, MALACCO E., POLI A., RAFTERY E.B., REID J.L., STUMPE K.O., ZANCHETTI A.
Comparison of a vasodilating beta-blocker and a cardioselective beta-blocker in long term treatment of hypertension: an European multicentre study
J. Hypertension (1989) 7 (suppl. 6): S266 - S267

52. (p)
CANONICO P.L., SORTINO M.A., **MAILLAND F.**
Meccanismo dell'azione anti-Parkinson della diidroergocriptina
Atti della XVI Riunione L.I.M.P.E.: simposio satellite "Rischi e benefici nel trattamento con agonisti recettoriali: la diidroergocriptina" -Palermo, novembre 1989

53. (p)
DE ALOYSIO D., BOTTIGLIONI F., JACOBELLIS M., **MAILLAND F.**
Lavanda vaginale a base di ciclopiroxolamina nel trattamento delle vaginiti micotiche
Giornale It. di Ostetricia e Ginecologia (1989) XI: 763-766

54. (p)
DE ALOYSIO D., BOTTIGLIONI F., JACOBELLIS M., **MAILLAND F.**
Dafnegin in ovuli e lavanda vaginale nel trattamento delle vulvovaginiti micotiche
Giornale It. di Ostetricia e Ginecologia (1989) XI: 937-942

55. (p)
CANONICO P.L., SORTINO M.A., **MAILLAND F.**
Diidroergocriptina e iperprolattinemie: rassegna sperimentale e clinica
Giornale it. di Ostetricia e Ginecologia (1990) XII: 395-400

56. (p)
FASCE V., VENTURINI P.L., GORLERO F., VALENZANO M., TEDESCHI C., ONGARI S., ZANOTTI A., **MAILLAND F.**, DE CECCO L.
Trattamento delle iperprolattinemie con diidroergocriptina: efficacia clinica e tollerabilità
Atti del IV Convegno Nazionale Aggiornamenti in Scienze Ginecologiche ed Ostetriche - Isola d'Elba, 3 - 10 giugno 1990

57. (p)
ZANOTTI A., COPPI G. and **MAILLAND F.**
Pharmacokinetics and pharmacodynamics of α-dihydroergokryptine in humans: single dose and steady state
In: Genazzani A.R., Petraglia F. and Volpe A. (eds): Progress in Gynecology and Obstetrics, pp. 491-499 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1990)

58. (p)
VOLPE A., MERCANTINI F., ADAMO R., ZANOTTI A., **MAILLAND F.** and GENAZZANI A.R.
Clinical evaluation of dihydroergokryptine in patients with functional hyperprolactinemia and microadenoma
In: Genazzani A.R., Petraglia F. and Volpe A. (eds): Progress in Gynecology and Obstetrics, pp. 527-531 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1990)

59. (p)
MAILLAND F., CANONICO P.L., ZANOTTI A.
Dihydroergokryptine and prolactin: clinical experience
In: Genazzani A.R., Petraglia F. and Volpe A. (eds): Progress in Gynecology and Obstetrics, pp. 479-489 (Carnforth, U.K. and Park Ridge N.J., U.S.A.: The Parthenon Publishing Group, 1990)

60. (p)
MAILLAND F., POLI A., ZOTTINO G.
La farmacovigilanza dell'indenololo in uno studio di coorte
Atti del Convegno "Farmacovigilanza: validità e problemi a confronto" - Torino 20 - 21 ottobre 1988. E.Genazzani (ed) Torino 1990

61. (p)
POLI A., **MAILLAND F.**
Metodologia di farmacovigilanza in uno studio di coorte su pazienti in menopausa in trattamento con una sostanza ad attività antiestrogenica
Giorn.it.ric.clin.ter.(1990) 11: 95-98

62. (p)
ILLENI M.T., BOMBELLI G., **MAILLAND F.**, PATTARINO P.L.
Effetto del PGT/1A sulla blastogenesi con mitogeni: studio ex vivo
La trasfusione del sangue (1991) 36 (Suppl 2): 256-260

63. (p)

MALACCO E., GROOTHOLD G., GNEMMI A.E., MAGENTA M., **MAILLAND F.**, NOIA E., SARTINI C., CORRADI L., FERRARIS G., FONTANA S., PIERATTI G., LUCCHELLI D., NICROSINI F., POZZA G. and TAGLIORETTI D.
An italian multicenter study on the metabolic effects of indenolol in hypertensive patients with non-insulin-dependent diabetes
Curr. Ther. Res. (1991) 49: 1034-1039

64. (p)
ILLENI M.T., BOMBELLI G., **MAILLAND F.**, PATTARINO P.P.
Effect of PGT/1A on blastogenesis with mitogens: an ex vivo study
J. Chemother. (1991) III (Suppl 3): 153-156

65. (p)
AGNOLI A., BUSSONE G., **MAILLAND F.**, MANZONI G.C., MARTUCCI N., NAPPI G.
Dihydroergokryptine vs flunarizine in the basic treatment of migraine without aura
Cephalalgia (1991) 11 (Suppl 11): 216-217

66. (p)
GROGNET J.M., ISTIN M., ZANOTTI A., **MAILLAND F.**, COPPI G.
Pharmacokinetics of alpha-dihydroergokryptine in monkeys after oral administration
Drugs exptl. clin. res. (1991) XVII (6): 309-312

67. (p)
GROGNET J.M., ISTIN M., ZANOTTI A., **MAILLAND F.**, COPPI G.
Pharmacokinetics of α-dihydroergokryptine in rats after intravenous and oral administration
Arzneim. Forsch. (1991) 41 (II), 7: 689-691

68. (p)
FREDIANI F., GRAZZI L., ZANOTTI A., **MAILLAND F.**, ZAPPACOSTA M., BUSSONE G.
Dihydroergokryptine versus dihydroergotamine in migraine prophylaxis: a double-blind clinical trial
Cephalalgia (1991) 11: 117-121

69. (p)
RODRIGUEZ M., **MAILLAND F.**, OBESO J.A., MARTINEZ LAGE J.M.
Dihydroergokryptine in Parkinson's disease: double blind study versus bromocriptine
Proceedings of the symposium: "Dihydroergokryptine a new dopamine-agonist", satellite of the European Conference on Parkinson's disease and extrapyramidal disorders, Rome, July 10-14, 1990

70. (p)
MAILLAND F., SIGNORELLI G., COPPI G.
Pidotimod, biological response modifier
Drugs of the future (1991) 16(12): 1096-1098

71. (p)
MAILLAND F.
Dihydroergocristin: Aktueller Stand von Forschung und Entwicklung
Arzneim.Forsch. (1992) 42 (11): 1379-1380

72. (p)
COPPI G., ZANOTTI A. und **MAILLAND F.**
Untersuchungen von Pharmacokinetik von Dihydroergocristin bei freiwilligen Probanden nach oraler Verabreichung von drei Formulierungen
Arzneim.Forsch. (1992) 42 (11): 1397-1399

73. (p)
BRAMANTI P., RICCI R.M., **MAILLAND F.**, DI PERRI R.
Wirkung von Dihydroergocristin auf kognitive Funktionen und Schlaf bei älteren Probanden
Arzneim.Forsch. (1992) 42 (11): 1403-1406

74. (p)
ADAMS K., ALLEN J.A., BROOKER P.C., JONES E., PROUDLOCK R.J., **MAILLAND F.** and COPPI G.
Evaluation of the mutagenicity of alpha-dihydroergokryptine in vitro and in vivo
Arzneim.Forsch. (1993) 43 (II): 1253-1257

75. (p)
NAPPI C., COLACE G., DI CARLO C., AFFINITO P., RUOTOLOC., MONTEMAGNO R., FARACE M., **MAILLAND F.** and DI RENZO G.F.
Effect of Dihydroergocryptine on serum prolactin levels and milk secretion in puerperal women
Gynecol. Endocrinol. (1993) 7: 1-5

76. (p)
MAILLAND F.
Pidotimod: einleitender Überblick
Arzneim.Forsch. (1994) 44 (II): 1399

77. (p)
COPPI G., AMICO ROXAS M., BERTE' F., BUSSI R., GNEMI P., HARLING R.J., **MAILLAND F.** et al.
Toxicological evaluation of pidotimod
Arzneim.Forsch. (1994) 44 (II): 1448-1453

78. (p)
ADAMS K., ALLEN J.A., BROOKER P.C., HENDERSON L., JONES E., PROUDLOK R.J., **MAILLAND F.**, COPPI G.
Genotoxicity testing of pidotimod in vitro and in vivo
Arzneim.Forsch. (1994) 44 (II): 1454-1459

79. (p)
MAILLAND F., COPPI G., SILINGARDI S.
Pharmacokinetics and oral bioavailability of pidotimod in humans
Arzneim.Forsch. (1994) 44 (II): 1465-1469

80. (p)
SPOTTI D., BIFFI M., COPPI G., SILINGARDI S. and **MAILLAND F.**
Pharmacokinetics of Pidotimod in Elderly Volunteers and in Renal Failure Patients
Arzneim.Forsch. (1994) 44 (II): 1470-1472

81. (p)
BUSSONE A., CERBO R., MARTUCCI N., **MAILLAND F.**, et al.
α-dihydroergocryptine in the prophylaxis of migraine: a multicenter double blind study versus flunarizine
Headache (1999) 39 (6): 426-431

82. (p)
BERGAMASCO B., FRATTOLA L., MURATORIO A., PICCOLI F., **MAILLAND F.**, PARNETTI L.
Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double blind, placebo-controlled study
Acta Neurol Scand (2000) 101: 372-380

83. (p)
MICIELI G., CAVALLINI A., MARCHESELLI S., **MAILLAND F.**, AMBROSOLI L. and NAPPI G.
Alpha-dihydroergocryptine and predictive factors in migraine prophylaxis
Int J Clin Pharmacol Ther (2001) 39: 144-151

84. (p)
MENDLING W. and **MAILLAND F.**
Microbiological and Pharmacological Profile of Nifuratel and its Favourable Risk/Benefit Ratio for the Treatment of Vulvo-vaginal Infections
Arzneim Forsch (2002) 52: 8-13

85. (p)
BARAN R., SPARAVIGNA A., SETARO M., **MAILLAND F.**
Computerized Image Analysis of Nails Affected by Fungal Infection: Evaluation Using Digital Photographs and Manually Defined Areas
J Drugs Dermatol (2004) 3(5):488-493

86. (p)
MONTI D., SACCOMANI L., CHETONI P., BURGALASSI S., SAETTONE M.F., **MAILLAND F.**
In vitro transungual permeation of ciclopirox from a hydroxypropyl chitosan-based, water soluble nail lacquer
Drug Development and Industrial Pharmacy (2005) 1:11-17

ABSTRACTS (DERMATOLOGY)

1. (a)
MONTI D., SACCOMANI L., CHETONI P., SAETTONE M.F., **MAILLAND F.**
Permeazione transungueale "in vitro" di ciclopirox da smalti medicati: effetto del tipo di veicolo
Proceedings of the 43° Simposio AFI 2003, Perugia, 11-13 giugno 2003

2. (a)
MONTI D., SACCOMANI L., CHETONI P., SAETTONE M.F., **MAILLAND F.**
Effect of nail lacquer composition on *in vitro* transungual permeation of ciclopirox
Proceedings of the 30th Annual Meeting of the Controlled Release Society, Glasgow, July 19-23rd, 2003

3. (a)
MAILLAND F.
Nuova tecnologia in film di biopolimeri idrosolubili per applicazione cutanea ed ungueale
Proceedings of the 79° Congresso Nazionale SIDeMaST, Castellaneta Marina (TA, Italy) 26-29 Maggio 2004

4. (a)
BARAN R. and **MAILLAND F.**
Transungual delivery of drugs: new perspectives
Proceedings of the 34th Annual European Society for Dermatological Research Meeting, Vienna, September 9-11th 2004, in J Investigative Dermatol (2004) 123:A74

5. (a)
BARAN R., SPARAVIGNA A., SETARO M., **MAILLAND F.**
Image analysis of nails affected by fungal infection
Proceedings of the International Society for Bioengineering and the Skin, Orlando, October 28-30th 2004

6. (a)
MONTI D., SACCOMANI L., TOGNATTI F., CHETONI P., BURGALASSI S., **MAILLAND F.**
Terbinafine based nail lacquers: *ex vivo* study on permeation through bovine hoof membranes
Proceedings of the 2nd EUFEPS Conference on Optimising drug delivery and Formulation: Evaluation of Drug Delivery Systems Issues and Perspectives, Versailles (France), Novembre 20-23rd, 2005

7. (a)
MONTI D., SACCOMANI L., CHETONI P., BURGALASSI S., **MAILLAND F.**
HPCH-based nail lacquers: "ex vivo" study on permeation of three antimycotics through bovine hoof membranes
Proceedings of the 5th World Meeting on Pharmaceutics and Pharmaceutical Technology, Geneva (Switzerland), March 27-30th 2006

8.(a)
BARAN R., **MAILLAND F.**, Frisenda L., Bergamini N.
A new topical treatment for onychomycosis - controlled study on the efficacy and safety of a new water-soluble ciclopirox formulation
Proceedings of the 16th Congress of the European Academy of Dermatology and Venereology, Vienna (Austria), May 16-20th, 2007

9.(a)
LEGORA M., **MAILLAND F.**
Structure and mechanism of adherence to nail surface of a film formed by Hydroxypropyl Chitosan
Proceedings of the 16th Congress of the European Academy of Dermatology and Venereology, Vienna (Austria), May 16-20th, 2007

10.(a)
SPARAVIGNA A., **MAILLAND F.**, SETARO M.
Assessment of the film forming, protective and penetration-enhancing activity of water soluble biopolymers on ungual laminae
Proceedings of the 16th Congress of the European Academy of Dermatology and Venereology, Vienna (Austria), May 16-20th, 2007

11.(a)
MAILLAND F., WENK J.
Antifungal activity of a new ciclopirox water soluble nail lacquer in *in vitro* models of onychomycosis
Proceedings of the 41st Annual Meeeting of the German-speaking Mycological Society, Berlin (Germany) September 6-8th, 2007
Mycoses (2007) 50 (Suppl 5):362

12.(a)
Sparavigna A., Setaro M., **MAILLAND F.**
Computerized Image Analysis in the Assessment of Human Nail Growth Rate
Proceedings of the 37th Annual European Society for Dermatological Research Meeting, Zürich (Switzerland) September 5-8th, 2007
J Invest Dermatol (2007) 127(Suppl 2):S20

13.(a)
MAILLAND F., MONTI D., SACCOMANI L., MUCCI E., GHELARDI E.
Antimycotic activity of subungual fluids as a proof of *in vitro* efficacious nail permeation by antimycotic nail lacquers
Proceedings of the 37th Annual European Society for Dermatological Research Meeting, Zürich (Switzerland) September 5-8th, 2007
J Invest Dermatol (2007) 127(Suppl 2):S22

14.(a)
MONTI D., SACCOMANI L., CHETONI P., BURGALASSI S., **MAILLAND F.**
Development of a drug permeation model through human infected nails and relationship with bovine hoof slices
Proceedings of the 37th Annual European Society for Dermatological Research Meeting, Zürich (Switzerland) September 5-8th, 2007
J Invest Dermatol (2007) 127(Suppl 2):S64

15.(a)
BARAN R., SPARAVIGNA A., SETARO M., **MAILLAND F.**, FRISENDA L.
Hidroxypropyl-chitosan accelerates nail growth both in healthy fingernails and in mycotic toenails
Proceedings of the 21st World Congress of Dermatology, Buenos Aires (Argentina) September 30th- October 5th, 2007

16.(a)
MAILLAND F., DAL BO L.
In vitro antifungal activity and model of nail permeation of ciclopirox in a hydroxypropyl-chitosan nail lacquer
Proceedings of the 21st World Congress of Dermatology, Buenos Aires (Argentina) September 30th- October 5th, 2007

17.(a)
MAILLAND F., DAL BO L. FRISENDA L.
Ciclopirox nail concentrations *in vitro* and after single and multiple applications on healthy fingernails of a hidroxypropyl-chitosan based nail lacquer
Proceedings of the 21st World Congress of Dermatology, Buenos Aires (Argentina) September 30th- October 5th, 2007

18.(a)
MAILLAND F., BARAN R.
Sensitivity of T.rubrum versus other dermatophytes to two ciclopirox nail lacquers in patients with onychomycosis
Proceedings of the 66th annual meeting of the American Academy of Dermatology, San Antonio (TX, US) February 1st-5th, 2008

19.(a)
MASCARUCCI P., **MAILLAND F.**
Availability of antimycotic agents into the nail plate after repeated application of nail lacquers to healthy human fingernails
Proceedings of the International Investigative Dermatology, Kyoto (Japan) May 14th-17th, 2008

20. (a)
FRISENDA L., **MAILLAND F.**, CANTORESI F.
Effect of a water soluble nail lacquer on human damaged nails
Proceedings of the VIth World Congress of the International Academy of Cosmetic Dermatology, Lisbon (Portugal) June 18th-20th, 2008

Enclosure 1

Baran and Dawber's
Diseases of the Nails and their Management

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stippled aspect of the nail reflects the camera flash and is clearly evident on photography. Alopecia areata may occur in association with both types.

Oral administration of biotin for 6 months resulted in a reduction of longitudinal ridging, thinning and distal notching of the nail plate in two cases of trachyonychia of childhood (Möhrenschlager *et al.* 1998).

A beneficial response following a short course of topically applied 5% 5-fluorouracil cream is anecdotal (Schissel & Elston 1998).

References

Achten, G. & Wanet-Rouard, J.J. (1974) Atrophie unguéale et trachyonychie. *Archives Belges Dermatologique* 30, 201.

Alkiewicz, J. (1950) Trachyonychie. *Annales de Dermatologie et de Syphiligraphie* 10, 136.

Arias, A.M., Yung, C.W., Rendler, S. *et al.* (1982) Familial severe twenty-nail dystrophy. *Journal of the American Academy of Dermatology* 7, 349.

Baran, R. (1981) Twenty-nail dystrophy of alopecia areata. *Archives of Dermatology* 117, 1.

Baran, R. & Dupré, A. (1977) Vertical striated sandpaper nails. *Archives of Dermatology* 113, 1613.

James, W.D., Odom, R.B. & Horm, R.T. (1981) Twenty-nail dystrophy and ichthyosis vulgaris. *Archives of Dermatology* 117, 316.

Leong, A.B., Gange, R.W. & O'Connor, R.D. (1982) Twenty-nail dystrophy (trachyonychia) associated with selective IgA deficiency. *Pediatrics* 100, 418.

Möhrenschlager, M., Schmidt, T., Ring, J. *et al.* (1998) Effects of biotin in trachyonychia of childhood. *Annales de Dermatologie et de Vénéréologie* 125 (Suppl. 1), 176.

Peloro, T.M. & Pride, H.B. (1999) Twenty-nail dystrophy and vitiligo: a rare association. *Journal of the American Academy of Dermatology* 40, 488–490.

Richert, B. & André, J. (1999) Trachyonychia: a clinical and histological study of 22 cases. *Journal of the European Academy of Dermatology and Venereology* 12 (Suppl. 2), S126.

Runne, V. (1980) Twenty-nail dystrophy with knuckle pads. *Zeitschrift für Hautkrankheiten* 55, 901.

Samman, P.D. (1979) Trachyonychia (rough nails). *British Journal of Dermatology* 101, 701.

Schissel, D.J. & Elston, D.M. (1998) Topical 5-fluorouracil treatment for psoriatic trachyonychia. *Cutis* 62, 27–28.

Tosti, A., Fanti, P.A., Morelli, R. *et al.* (1991) Spongiotic trachyonychia. *Archives of Dermatology* 127, 584–585.

Pseudomycotic nail dystrophy (pseudomycotic onychia)

Four cases of isolated pseudomycotic nail dystrophy were studied by Higashi *et al.* (1997). All the fingernails and toenails were simultaneously involved. Clinical features include longitudinal striations, fissuring and scaling of the surface of the nail plate with sometimes a yellow-brown discoloration.

The epithelium of the nail matrix reveals hyperplasia with a granular layer and projections similar to the crest of a wave. Inflammatory cell infiltration is present at the upper dermis of the matrix. The nail plate consists of normally keratinized layers and abnormal ones in stratiform pattern.

These findings differ histologically from that of psoriasis, lichen planus and twenty-nail dystrophy. Because of the inflammatory response of the matrix, Higashi *et al.* (1997) suggest the term 'pseudomycotic onychia'. The significance of isolated pseudomycotic nail dystrophy is not known; however it seems difficult to completely rule out alopecia areata restricted to the nail, a condition where the severe changes are sometimes 'simulating longstanding onychomycosis' (Demis & Weiner 1963). Milligan *et al.* (1988) have reported two cases involving all the digits, associated with vitiligo.

References

Demis, D.J. & Weiner, M.A. (1963) Alopecia universalis, onychodystrophy and total vitiligo. *Archives of Dermatology* 88, 195–201.

Higashi, N., Kume, A., Ueda, K. *et al.* (1997) Clinical and histopathological study of pseudo-mycotic onychia. *Hifu* 39, 469–474.

Milligan, A., Barth, J.H., Graham-Brown, R.A.C. & Dawber, R.P.R. (1988) Pseudo-mycotic nail dystrophy and vitiligo. *Clinical and Experimental Dermatology* 13, 109–110.

Lamellar nail splitting (onychoschizia lamellina)

In this condition, found in 27–35% of normal adult women, the distal portion of the nail splits horizontally (Fig. 2.31). The nail is formed in layers analogous to the formation of scales in the skin; the thin lamellae then break off. Exogenous factors contribute to the defect. It is common in people who carry out a great deal of housework, whose nails are repeatedly soaked in water and then dried. Splitting into layers has been reported in X-linked dominant chondrodysplasia punctata (Happle

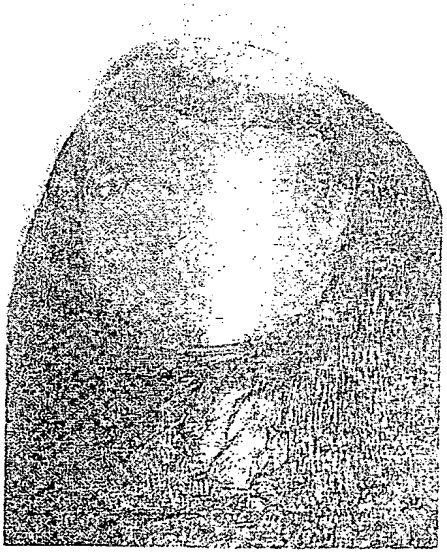

Fig. 2.31 Onychoschizia lamellina (lamellar splitting).

(a) (b)

Fig. 2.32 (a,b) Elkonyxis.

1979) and in polycythaemia vera (Graham-Brown & Homes 1980). In lichen planus, and in psoriasis treated with systemic retinoids, onychoschizia may be seen in the proximal portion of the nail (Baran 1990).

Shelley and Shelley (1984) studied with scanning electron microscopy the distal ends of nails of four women presenting with onychoschizia. The dorsal surface and tip of each nail showed horizontal lamellar separations representing single cell layers. Some cleavage lines extended proximally into the nail plate, revealing remarkable sculptured cell surfaces deep within the plate. These observations indicate that the lamellar splitting of onychoschizia occurs between cell layers. This presumably results from repeated trauma to a nail with diminished adherence between cell layers, secondary to the dissolution of intercellular cement by detergents and nail polish solvent.

Wallis *et al.* (1991) studied the *in vitro* nail changes produced by several organic solvents, detergents, other polar materials, and both acidic and basic solutions. Although other factors may influence onychoschizia, the typical changes can be produced in normal nails after a 21-day challenge of repeated exposure to water followed by dehydration. Scanning electron microscopy demonstrated unattached individual cells in empty spaces in which separation was prominent. The prominent *in vitro* changes from wetting and drying suggest that lamellar dystrophy could be managed by hydration followed by an occlusive topical agent that promotes water retention. Wallis *et al.* (1991) have successfully combined protection from exposure with hydrophilic petrolatum (Aquaphor), as a nail cream applied to the wet nails to maintain a relatively constant level of hydration. α-Hydroxy acids are more than mere moisturizers according to Leyden *et al.* (1995).

References

Baran, R. (1990) Retinoids and the nails. *Journal of Dermatological Treatment* 1, 151–154.

Graham-Brown, R.A.C. & Homes, R. (1980) Polycythaemia rubra vera with lamellar dystrophy of the nails, a report of two cases. *Clinical and Experimental Dermatology* 5, 209.

Happle, R. (1979) X-linked dominant chondrodysplasia punctata. *Humangenitik* 53, 65.

Leyden, J.J., Lavker, R.M., Grove, G. *et al.* (1995) Alpha hydroxy acids are more than moisturizers. *Journal of Geriatric Dermatology* 3 (Suppl. A), 33A–37A.

Shelley, W.B. & Shelley, E.D. (1984) Onychoschizia, scanning electron microscopy. *Journal of the American Academy of Dermatology* 10, 623–627.

Wallis, M.S., Bowen, W.R. & Guin, J.R. (1991) Pathogenesis of onychoschizia (lamellar dystrophy). *Journal of the American Academy of Dermatology* 24, 44–48.

Elkonyxis (Fig. 2.32)

Initially the nail appears punched out at the lunula and subsequently the disorder moves distally with the growth of the nail. It has been described in secondary syphilis, psoriasis, Reiter's syndrome and after trauma. It may be produced by etretinate (Cannata & Gambetti 1990).

Reference

Cannata, G. & Gambetti, M. (1990) Elconyxis, une complication inconnue de l'étrétinate. *Nouvelles Dermatologiques* 9, 251.

Enclosure 2

Baran and Dawber's
Diseases of the Nails and their Management

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In this chapter the onychomycoses are considered in detail, together with a variety of infections occasionally seen in and around the nail apparatus; some infections (see chapter contents above) are discussed, where appropriate, in other chapters.

Onychomycoses occur throughout the world but there are regional differences in incidence. Precise data as to their prevalence have only recently become available and the results again vary from country to country (Baran *et al.* 1999). The results also vary with the method of calculation of the prevalences. For instance Roberts (1992) found that by using a photographic identification method in randomly selected individuals, about 2.3% of subjects in the UK had changes in their nails compatible with onychomycosis. However, larger numbers have been found by direct examination of populations attending dermatologists in the USA and in Finland. Specific groups such as diabetics have also been found to have a higher prevalence than normal individuals (Gupta *et al.* 1998a). Sociocultural and occupational factors play an important part in the increase as well as the spread of organisms such as *Trichophyton rubrum*. In rural areas in Zaire, the incidence was found to be 0.89%, whereas in city dwellers it was 4% in men and 2.8% in women (Vanbreuseghem 1977). Fungal infections of the nails have been reported in 6.5–27% of miners (Götz & Hantschke 1965). Some 1.5% of all patients attending dermatological centres have onychomycosis (Achten & Wanet-Rouard 1981). Between 18% and 40% of all nail disorders are onychomycoses (Pardo-Castello & Pardo 1960; Achten & Wanet-Rouard 1978) and 30% of all dermatomycoses are nail infections (Langer 1957).

Onychomycosis

Fungal infections of the nail apparatus may be classified as superficial, distal or proximal according to the site of fungal invasion (Fig. 4.1). In this chapter a new classification (Baran *et al.* 1998b) is used, which expands on previous schemes to include mycoses involving the whole nail apparatus as well as a new form, endonyx onychomycosis. The appearance of the lesion may provide clues to the likely identity of the infecting organism, although it is seldom possible to identify the species on clinical grounds alone: for instance, irrespective of right or left handedness, unilateral hand involvement is a common feature of dermatophytosis caused by *Trichophyton rubrum*; in such patients both feet are commonly infected (Vazquez *et al.* 1998) (Fig. 4.2). Similarly onychomycosis confined to the fingernails is more suggestive of a *Candida* infection, especially in paronychia and onycholysis, although infections caused by either *Scytalidium dimidiatum* (*Hendersonula toruloidea*) or *S. hyalinum* may both produce identical nail lesions. These observations contribute to the process of making the diagnosis, but this will depend ultimately on the laboratory identification of the fungus. Invasive onychomycosis can also be proved convincingly by histology. A search for infections at other sites such as the hands, feet (soles and webs) or groins, or the scalp in infants, should be instituted when there is a suspicion of onychomycosis. Discoloured dyschromic nail changes caused by fungi are considered in the section on chromonychia (page 89).

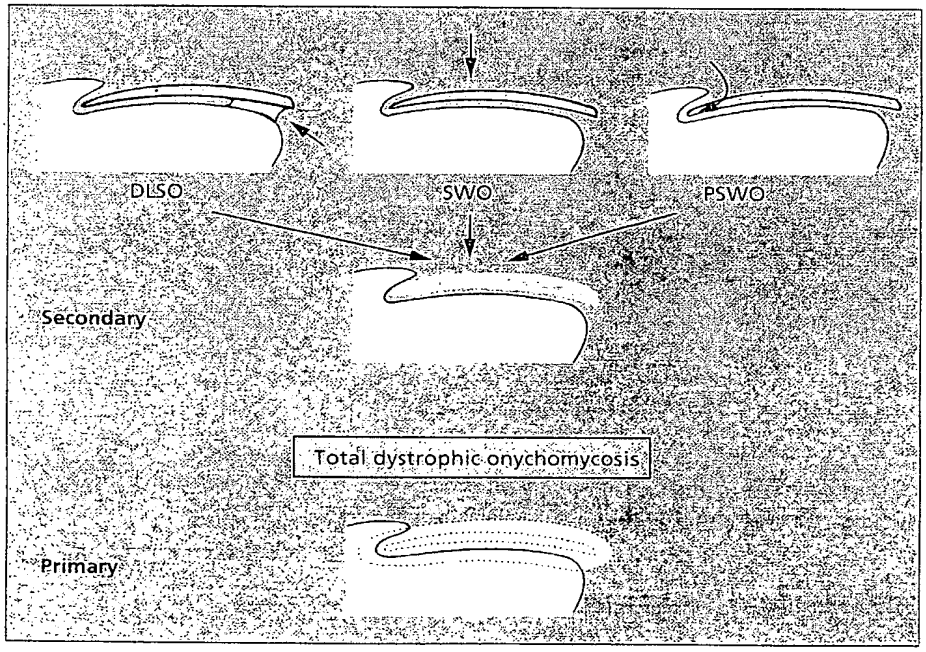


Fig. 4.1 Diagram to show the site of invasion and types of onychomycosis. DLSO, Distal and lateral subungual onychomycosis; EO, endonyx onychomycosis; PSWO, proximal subungual white onychomycosis; SWO, superficial white onychomycosis.

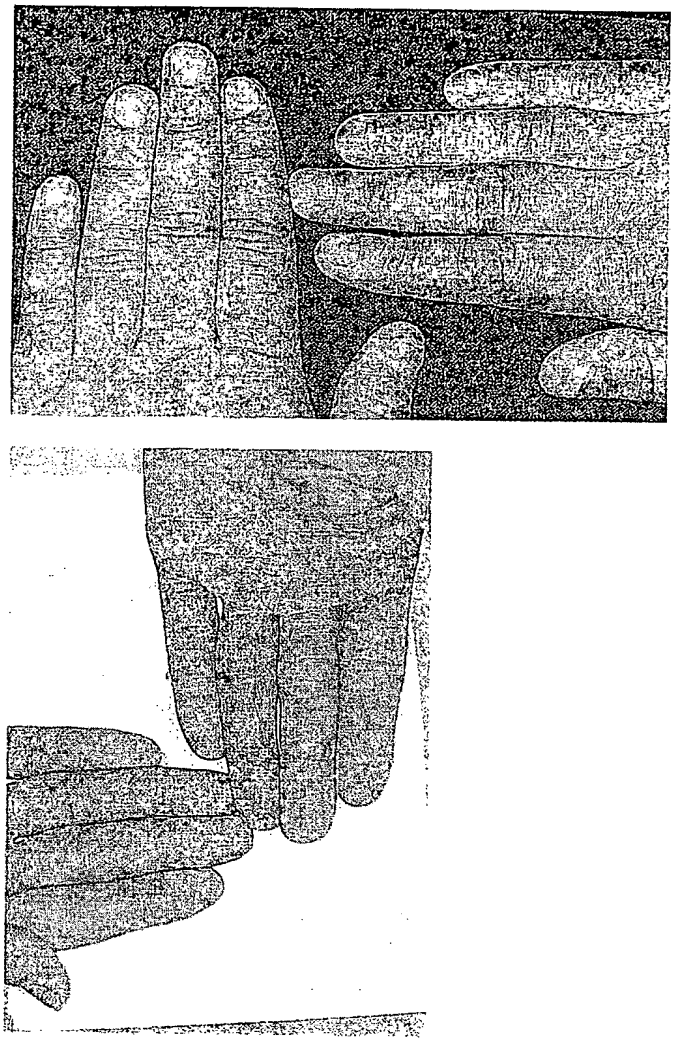


Fig. 4.2 (a) Distal and lateral subungual onychomycosis presenting as one hand/two-foot tinea syndrome. (b) Involvement of the palm of the same hand.

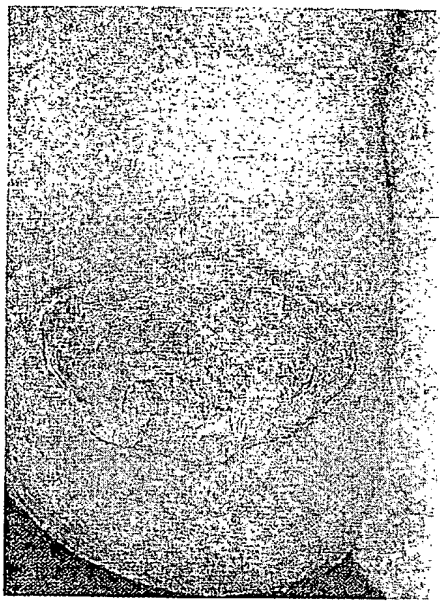


Fig. 4.3 Distal and lateral subungual onychomycosis due to *Trichophyton rubrum*.

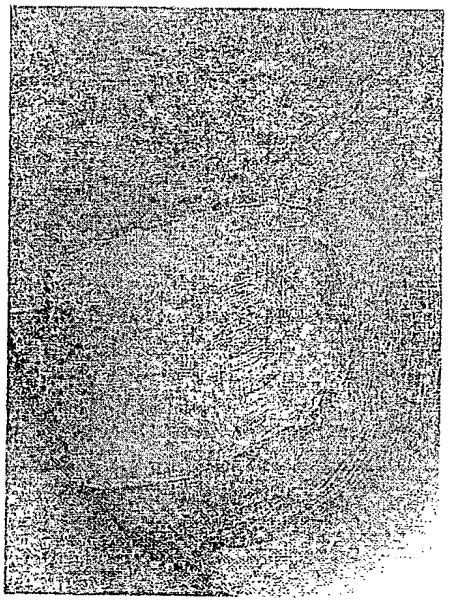


Fig. 4.4 Distal and lateral subungual onychomycosis restricted to the medial edge due to *Trichophyton (mentagrophytes* var.*) interdigitale*.

Distal and lateral subungual onychomycosis (Figs 4.3–4.10)

Primary distal and lateral subungual onychomycosis (Table 4.1)

In this pattern of infection the onychodermal band is disrupted by infection and the fungus reaches the underside of the nail via the hyponychium, the nail bed, or the lateral nail fold where the stratum corneum is invaded. The nail bed infection in distal and lateral subungual onychomycosis (DLSO) caused by *T. rubrum* is the result of the fungus spreading from the plantar (Evans 1998) and palmar surface of the feet and hands, a pattern seen in the one-hand/two-foot tinea syndrome (Daniel *et al.* 1997). The thickened horny layer raises the free edge of the nail plate with disruption of the normal nail plate–nail bed attachment (Baran *et al.* 1998a). The disease spreads proximally and the nail becomes opaque. Fungal invasion leads to orthokeratosis of the nail bed epithelium. In advanced nail disease a more severe inflammatory reaction affects the nail bed with penetration of mononuclear cells and polymorphonuclear leucocytes into the subungual keratin, sometimes mimicking Munro's microabscesses. Parakeratotic foci, often containing inspissated serum, may appear (Haneke 1991). In time, tunnels produced by dermatophytes and containing air, described by Alkiewicz (1948) as a transverse net, appear as opaque streaks in the nail plate. Occasionally, this may be seen more clearly

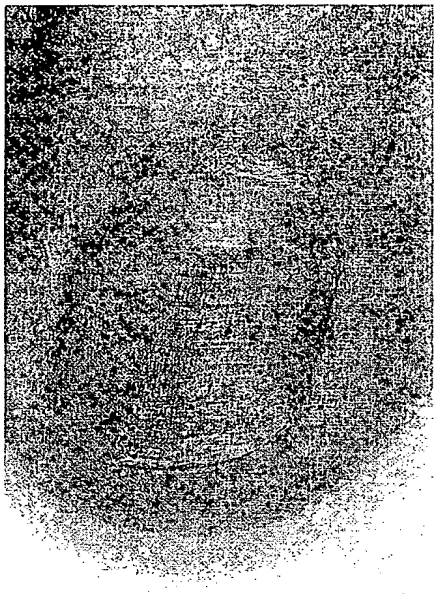


Fig. 4.5 Distal and lateral subungual onychomycosis due to *Trichophyton rubrum nigricans* presenting with longitudinal melanonychia.

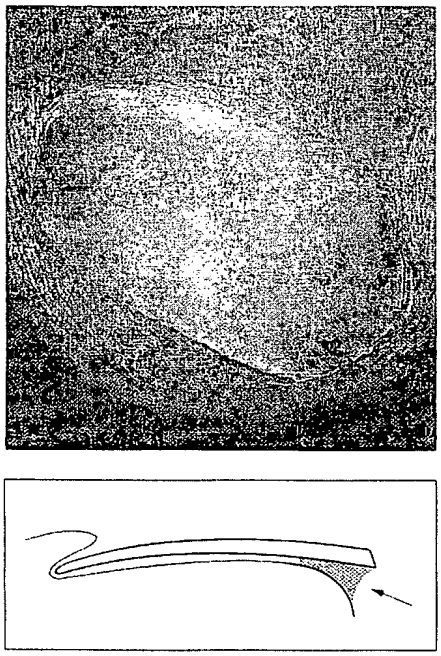


Fig. 4.6 Onycholysis due to *Trichophyton rubrum*.

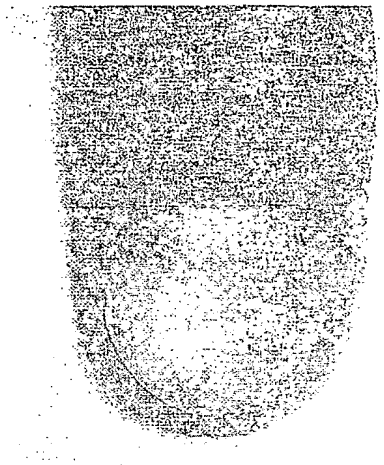


Fig. 4.7 Onycholysis due to *Trichophyton rubrum*.

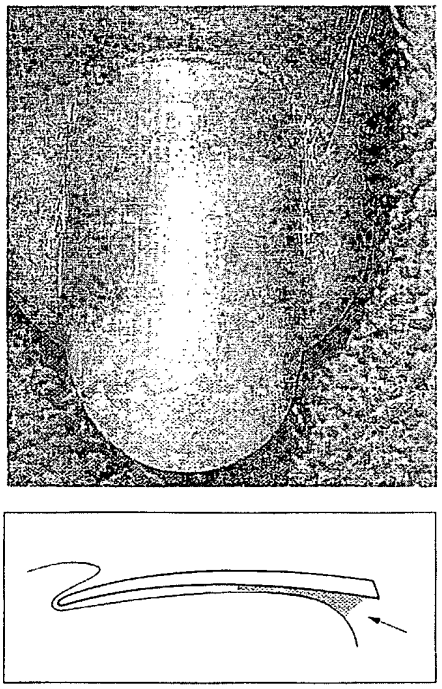


Fig. 4.8 Onycholysis due to *Candida albicans*.

with the aid of a lens, after the nail plate has been treated with cedar oil to render it translucent. Where the network is sufficiently dense, it appears as an opaque white or yellowish zone or streak, a clinical feature often seen in dermatophyte or mould infections. Such lacunae often contain masses of fungi as well as keratin debris and their existence provides a difficult target for treatment as persistence of infection may occur at this site, possibly due to poor drug penetration. Often there is nail invasion in a longitudinal narrow band which follows the ridges of the nail bed. In addition according to Zaias (1972), a variety of microorganisms may coexist in the ecological niche created by an area of onycholysis and these are responsible for colour changes which vary from grey to chestnut brown. Negroni (1976) has reported on nail erythrasma. With progressive infection, the nail becomes friable and eroded at the lateral and distal borders.

The clinical appearances of nail dystrophies caused by different fungi are seldom diagnostic, but there may be some useful and potentially distinctive features apart from the differences in

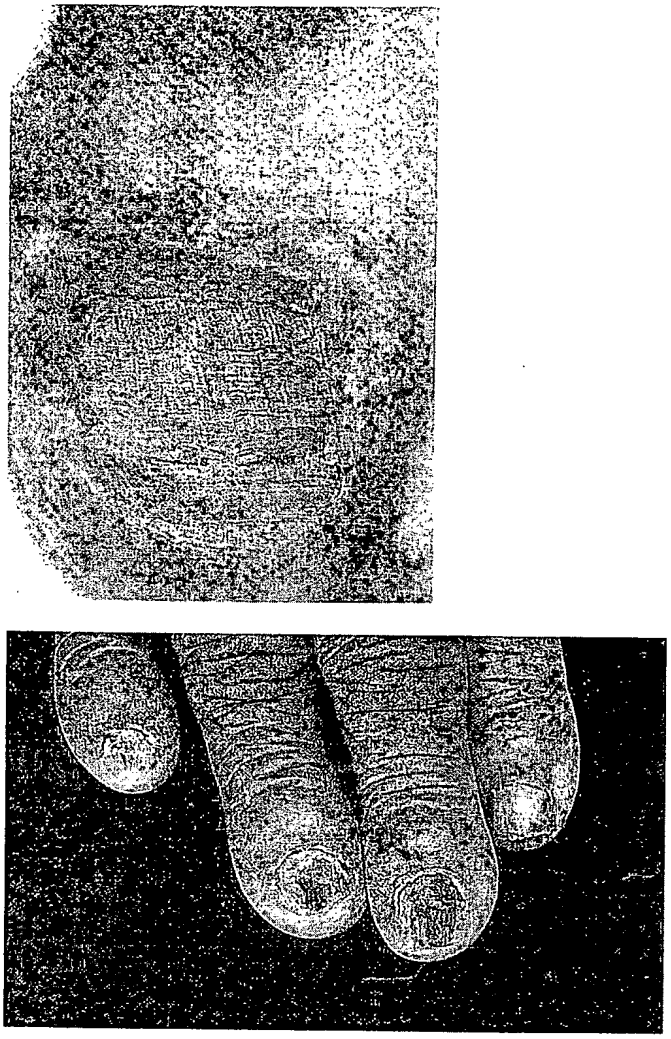


Fig. 4.9 (a) Distal and lateral subungual onychomycosis (DLSO) due to *Scytalidium dimidiatum* in a Caucasian patient. (Courtesy of D. Jones UK.) (b) DLSO associated with paronychia due to *S. dimidiatum*.

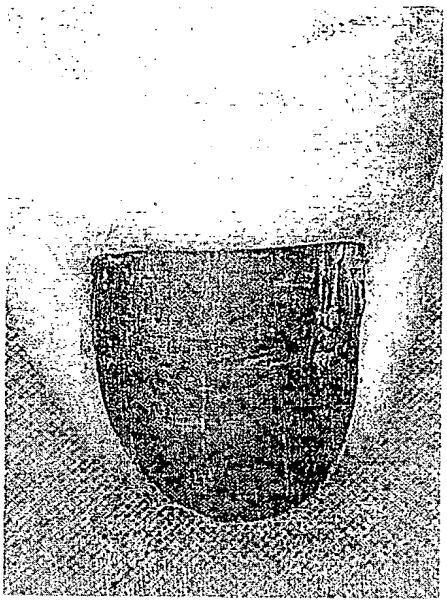


Fig. 4.10 Black nail due to *Candida parapsilosis*. (Courtesy of O. Binet, France.)

Table 4.1 Causes of distal and lateral subungual onychomycosis (DLSO).

Dermatophytes	*Trichophyton rubrum, T. interdigitale, Epidermophyton floccosum, T. schoenleinii, T. tonsurans, T. soudanense, T. erinacei, T. verrucosum, T. concentricum, T. violaceum, M. canis*
Yeasts	*Candida albicans, C. parapsilosis*
Moulds	*Scopulariopsis brevicaulis, Scytalidium dimidiatum, S. hyalinum*

the overall pattern of nail involvement discussed previously. For example hyperkeratosis accompanying onycholysis is a common feature of dermatophyte infections, which are the commonest causes of DLSO, whereas in *Candida* onychomycosis, gross hyperkeratosis is mainly seen in total nail plate involvement in patients with chronic mucocutaneous candidiasis; in other cases of true *Candida* onychomycosis thickening of the nail plate may be minimal. There has been some debate about the role of *Candida* as a cause of DLSO. *Candida* species are said not to produce specific keratinases and therefore they cannot invade the healthy nail plate. There does appear to be a group of patients in whom there is genuine distal and lateral invasion of the nail plate with erosion, confirmed histologically, but without significant thickening. This is mainly seen in women, patients with endogenous or exogenous Cushing's syndrome or those with Raynaud's phenomenon (Hay *et al.* 1988c). It may also occur in some tropical countries. While it is possible that some invasion is secondary to pre-existing onycholysis (see below), this is seldom possible to establish. There is often a distinctive brown- or cinnamon-coloured discoloration of nails, mainly toenails, affected by *Scopulariopsis brevicaulis*. It is caused by the presence of large numbers of pigmented conidia produced *in situ* (Belsan & Fragner 1965). Likewise brown pigmentation appearing as an irregular streak in the nail plate, often at the lateral border of the great toenail, is also a feature of infections caused by *Trichophyton interdigitale* and *T. rubrum* may sometimes present with longitudinal melanonychia (Higashi 1990; Perrin & Baran 1994). In this case the cause of the pigmentation is unknown. The nail dystrophies caused by *Scytalidium dimidiatum* (Fig. 4.9) or *Scytalidium hyalinum* are similar to dermatophyte onychomycosis (Moore 1978; Gugnani *et al.* 1986) and may be found in Caucasians (Jones *et al.* 1985). However, secondary paronychia appears to be

Table 4.2 Organisms found in distal lateral subungual onychomycosis (DLSO) with pre-existing onycholysis.

Dermatophytes	*Trichophyton rubrum, T. interdigitale, Epidermophyton floccosum*
Yeasts	*Candida albicans, C. parapsilosis, C. tropicalis*
Mould	Various species have been reported including *Aspergillus* and *Penicillium*

commoner in fingernail infections and extensive onycholysis may also be a prominent feature of these infections. This may lead to a transverse fracture of the nail plate near the proximal nail fold and subsequent shedding of the distal plate.

Distal and lateral subungual onychomycosis secondary to onycholysis (Table 4.2)

On occasions dermatophytes may be isolated from nails, such as the big toenail, which show idiopathic or primary onycholysis. Davies (1968) reported on 3955 samples of nails infected with *T. rubrum*. Nine per cent of the normal, healthy looking nails were positive for fungus on direct microscopy, culture or both. This was confirmed by Baran and Badillet (1982), who examined 46 samples of normal nails from patients infected in other sites with *T. rubrum* (35 cases), *T. interdigitale* (10 cases) (one patient having a mixed infection), and *Epidermophyton floccosum* (one case). *T. rubrum* was found in the nails of four of these patients, *T. interdigitale* in two and *E. floccosum* in one only. A subsequent control study was carried out on 52 outpatients seeking medical advice for reasons other than big toenail dystrophy. Dermatophytes were isolated from clinically normal big toenails in two patients, *T. rubrum* in one case and *E. floccosum* in the other. In these apparently healthy nails, the fungi were presumably acting as commensals rather than pathogens. However, they are potentially invasive, particularly in nails showing onycholysis, and may be transmitted to a different host. On the fingers, primary onycholysis is more frequently associated with secondary invasion by *Candida* and/or *Pseudomonas*. It is most common in women in whom there is repeated contact with water, soap and detergents. Contrary to the classical pattern of DLSO, which usually starts with distal hyperkeratosis, there is a reversal of the usual order of evolution of each lesion in secondary onychomycosis. For example, in the fingernails onycholysis precedes any subsequent thickening of the distal subungual area, hence the name of DLSO associated with onycholysis. Repeated episodes of friction secondary to rubbing of the nails against shoes or the repeated episodic trauma incurred during running or jogging may also create an area of traumatic onycholysis where microorganisms are also potentially but not invariably pathogenic. A variety of fungi not normally considered pathogenic may be isolated from dystrophic nails, particularly in the elderly (English & Atkinson 1974). The usual clinical pattern of nail involvement most closely resembles DLSO. Hyperkeratosis and brown or green discoloration are common and the toenails are most commonly affected. The organisms isolated may include *Aspergillus* species such as *A. terreus* or *A. versicolor*, *Acremonium* spp., *Penicillium* spp. and *Pyrenochaeta unguium hominis* (Punithaligam & English 1975). As these organisms do not appear to be able to break down keratin, it is assumed that they are colonists of dystrophic or abnormal nails. It is however difficult to be certain that they are not contributing to the nail dystrophy. There is some evidence that some of these species (e.g. *Acremonium* spp.) produce perforating organs, specialized hyphal structures usually associated with hair invasion, analogous to those seen in dermatophytosis. Other non-dermatophyte fungi invading nails such as *S. brevicaulis* can be demonstrated by electron microscopy inside keratinized cells (Achten *et al.* 1979). *Scytalidium* species, pathogenic in humans, produce keratinases.

Other yeasts may also be isolated from the same site. These include *Candida* species such as *C. guilliermondii*. As with the moulds discussed above, it is assumed that they are secondary invaders. The distinction between nail pathogens and opportunistic organisms which inhabit nails under abnormal conditions is a tenuous one. As has been seen above, even the dermatophytes can be secondary invaders (Baran & Badillet 1983). Likewise *S. brevicaulis* is often merely a colonist.

The clinical significance of nail invasion or colonization by fungi, which are not normally pathogenic, needs to be carefully considered in the light of laboratory findings such as the results of nail biopsy. It is likely that organisms which colonize nails may play a more destructive role if the host's immune defences or the nail matrix is altered by disease or another infection. Equally their removal may simply be 'academic' if the nail dystrophy remains after antifungal therapy.

Superficial onychomycosis

Superficial white onychomycosis (Figs 4.11–4.13, Table 4.3)

Superficial white onychomycosis (SWO) is fairly rare and is normally confined to the toenails.

Here the surface of the nail plate is the initial site of invasion. The causative organisms produce a clinical picture of small superficial white patches with distinct edges (Zaias 1966). These later coalesce and may gradually cover the whole nail, hence the term leuconychia trichophytica (mycotica). The chalky white surface becomes roughened and the texture softer than normal. The appearance has been likened to 'paper-bark' (McAleer 1981), the affected nail plate crumbles easily and old lesions acquire a yellowish colour. The upper surface of the nail plate is the primary site of the fungal invasion. This type of nail invasion is caused by *T. interdigitale* (*mentagrophytes*) in more than 90% of the cases. Using epi-illumination microscopy the individual white flakes representing colonies of *T. interdigitale* can be observed clearly. Patches of SWO are not uncommonly

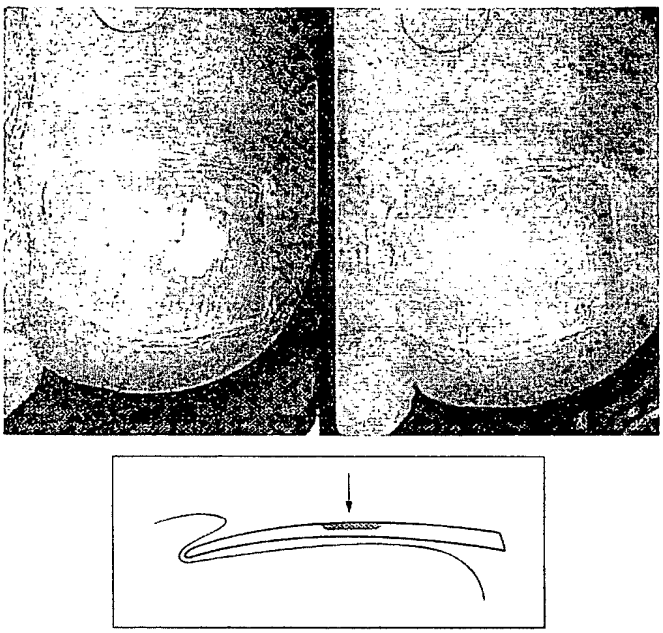


Fig. 4.11 Superficial white onychomycosis due *to Trichophyton interdigitale*. (a) Before scraping. (b) After superficial scraping.

Fig. 4.12 Superficial white onychomycosis due to *Aspergillus* spp. (a) Before scraping. (b) After scraping.

seen in areas where the nail is occluded, for instance by an overlying adjacent toe. Infections caused by non-dermatophytes such as *Aspergillus terreus*, *Fusarium oxysporum* or *Acremonium* spp. are more often seen in patients in a tropical or subtropical environment. *Candida albicans* has occasionally been isolated in infants (Zaias 1990a).

Superficial black onychomycosis (Fig. 4.14)

A similar pattern of nail plate invasion and dystrophy may be caused by dematiaceous or black fungi. These are rare but the following have been described as possible causes: *S. dimidiatum* (Badillet 1988; Meisel & Quadripur 1992); *T. rubrum* (Badillet 1988).

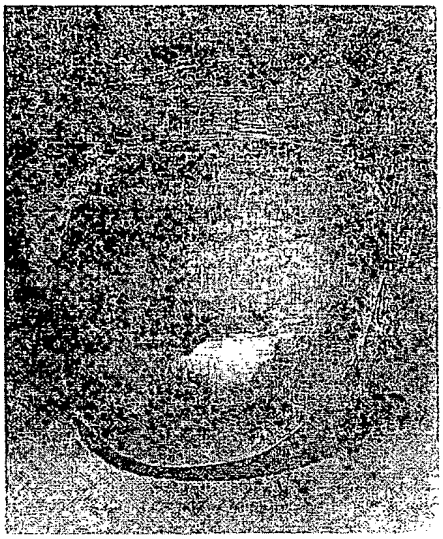


Fig. 4.13 Superficial white onychomycosis associated with distal and lateral subungual onychomycosis due to *Trichophyton interdigitale*.

Table 4.3 Causes of superficial white onychomycosis (SWO).

Dermatophytes	*Trichophyton interdigitale* (*Microsporum persicolor*, *T. rubrum* * and *T. equinum*)
Yeasts	*Candida albicans* (only in infants, Zaias 1990a)
Moulds	*Acremonium* and *Fusarium* spp., *Aspergillus terreus*

* In this case fungal elements are found deep in the nail plate.

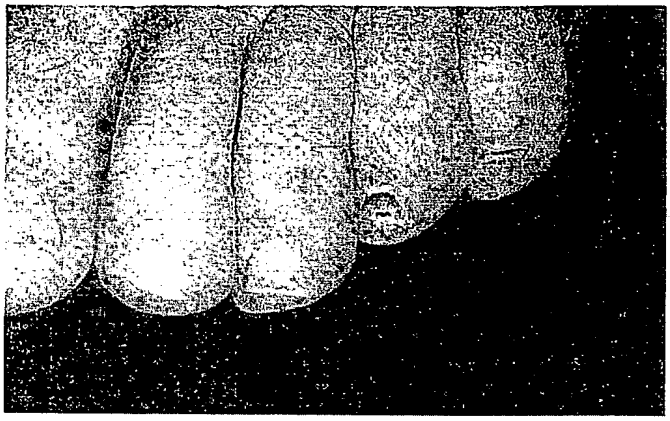
Variants of superficial white onychomycosis

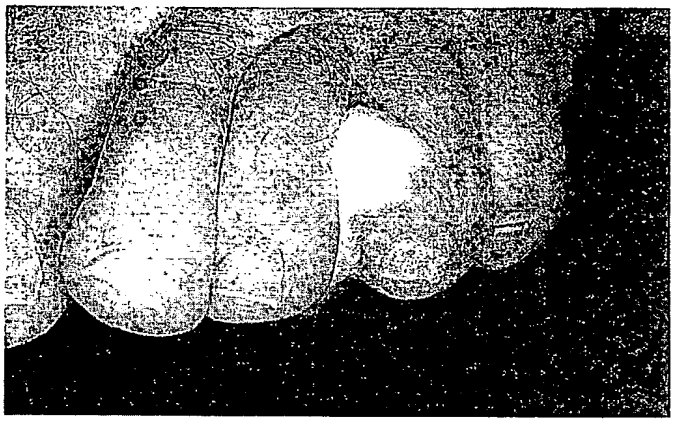
In HIV-infected patients SWO is not rare in finger or toenails and is due to *T. rubrum* (Chapter 6). However, here the pattern of infection is different, as there is often proximal subungual infection as well (see below).

Endonyx onychomycosis (Fig. 4.15)

In endonyx onychomycosis (EO) infections of the fingernails due to the dermatophytes which cause endothrix scalp infections may present with less nail plate thickening, but the plate is pitted and the distal margin covered with lamellar splits (Kalter & Hay 1988). These changes have been studied in detail by Tosti *et al.* (1999) and shown to consist of areas of superficial nail plate invasion but with deep penetration, and fungal hyphae are seen within the nail plate. The nail surface has lamellar-like splits and the end of the nail plate is often friable and split. However, hyperkeratosis is minimal and dense opacification is unusual. These changes are typical of invasion caused by *Trichophyton soudanense* but similar changes have been seen with *T. violaceum*.

(a)





(b)

Fig. 4.14 Superficial black onychomycosis due to *Scytalidium dimidiatum*. (a) Before scraping. (Courtesy of G. Badillet, France.) (b) After superficial scraping.

Fig. 4.15 Endonyx onychomycosis due to *Trichophyton soudanense*.

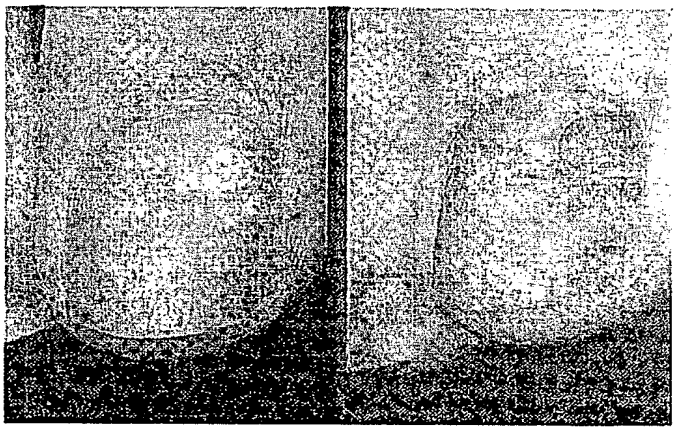
Proximal subungual onychomycosis

Proximal white subungual onychomycosis (Figs 4.16–4.18)

Proximal white subungual onychomycosis (PWSO) is rare and affects both fingernails and toenails. This clinical pattern of nail invasion is very rare. The causative organisms penetrate via the proximal nail fold, the stratum corneum of which is the primary site of the fungal invasion. When reaching the matrix the fungus invades the undersurface of the nail plate. A white spot appears from beneath the proximal nail fold and, although it is confined initially to the lunula area, when the white spot moves distally, it still remains in the same layer of the nail plate. The fungus has to invade more distal parts of the matrix to get entrapped in the deeper layers of the nail plate. This is sometimes accompanied by slight discomfort. This pattern may also be seen where there is a recurrence of nail infection in an incompletely treated nail.

This type of nail invasion is usually caused by *T. rubrum*; but *T. megnini*, *T. schoenleinii* or *E. floccosum* may be seen.

Recently a rapidly developing form of PWSO has been recorded in patients with AIDS. Here the infection may spread rapidly under the nail from the proximal margin of all the finger and toenails (Dompmartin *et al.* 1990). Histopathology shows that the entire nail plate is infiltrated with fungi, which are lying in a longitudinal parallel arrangement. However, the picture is complicated in that other surfaces such as the superior aspect of the plate and the distal or lateral margins may also be involved.



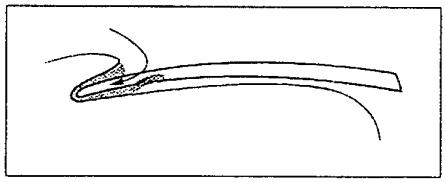


Fig. 4.16 (a) Proximal white subungual onychomycosis. (b) Biopsy restricted to the nail plate.

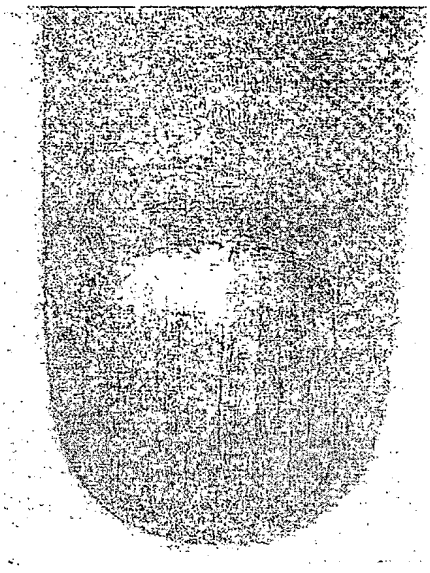


Fig. 4.17 Proximal white subungual onychomycosis with dystrophic keratin of the superficial nail plate.

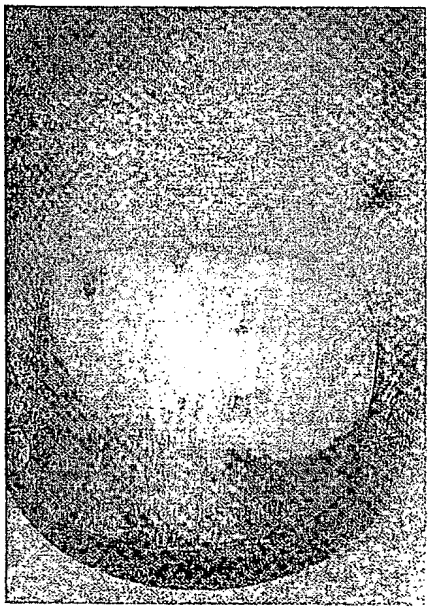
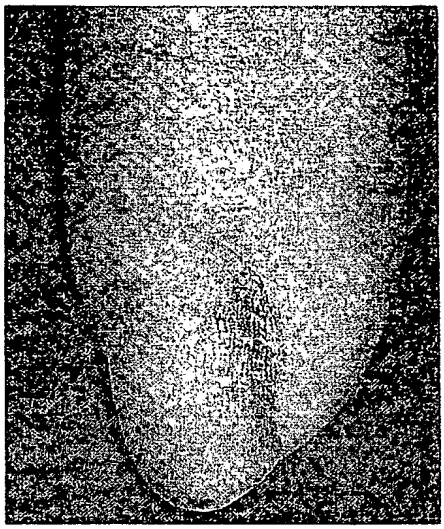


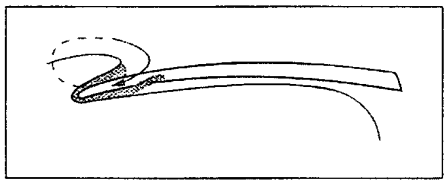
Fig. 4.18 Proximal white subungual onychomycosis in AIDS.

Possibly because of the rapid spread these patients do not show much nail thickening (Weismann *et al.* 1988).

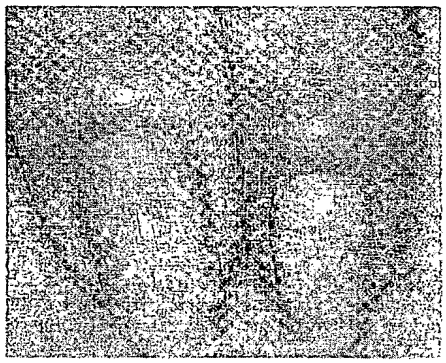
Proximal subungual onychomycosis secondary to paronychia (Fig. 4.19)

Paronychia is observed mainly in adult women and affects particularly the index, middle finger and thumb of the dominant hand. Frequent manual work with carbohydrate-containing foods and moisture, maceration, occlusion, hyperhidrosis and acrocyanosis favour the disease. In children, finger sucking is a





(a)



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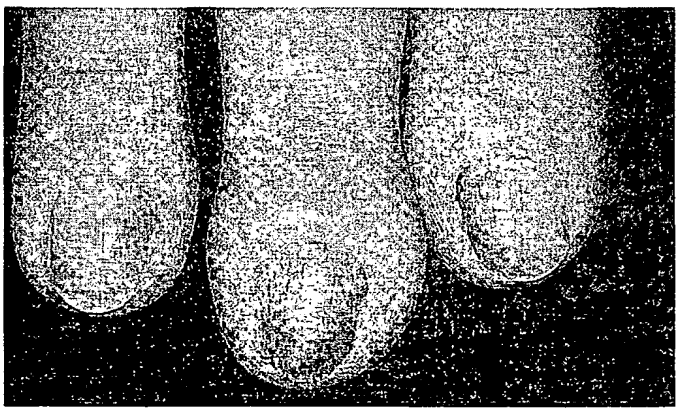
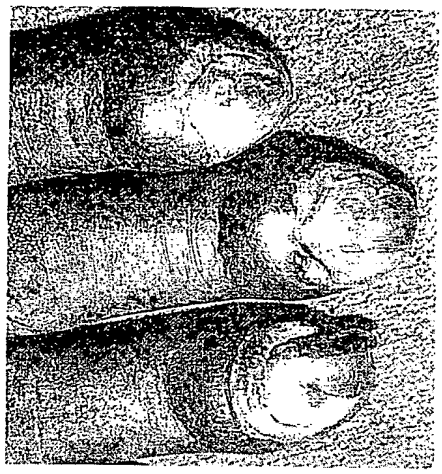
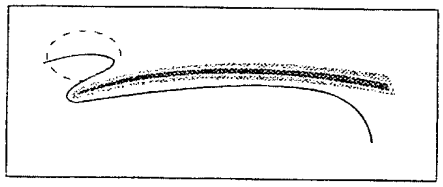


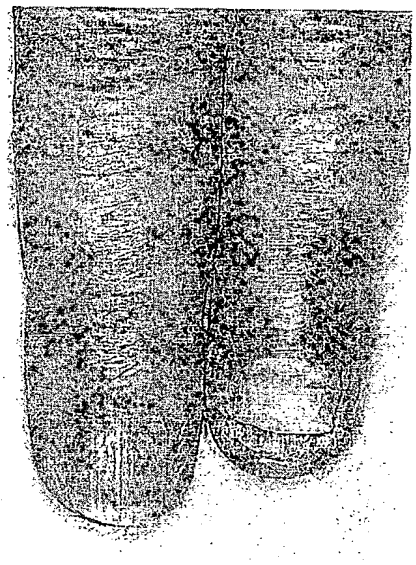
(c)

Fig. 4.19 (a) Proximal subungual onychomycosis secondary to chronic paronychia. (b) Early stage—normal nails. (c) Gross lateral periungual inflammation and swelling with early nail plate involvement of the lateral edges. (*continued p. 138*)

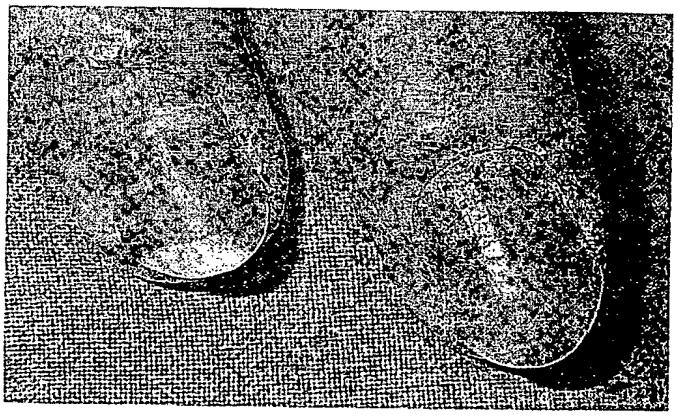


(d)





(e)



(f)

cause of paronychia (Stone & Mullins 1968). Diabetes mellitus and other hormonal disturbances and drugs such as corticosteroids, cytotoxics and antibiotics may exacerbate *Candida* paronychia. The first step in the development of chronic paronychia is mechanical infection or chemical trauma that produce cuticle damage. At that time the epidermal barrier of the ventral aspect of the proximal nail fold is destroyed and the area is suddenly exposed to a variety of environmental hazards. Irritants and allergens may then produce an inflammatory reaction of the nail fold and nail matrix, which interferes with the normal nail growth. Usually the nail fold inflammation affects the lateral portion of the matrix leading to nail plate deformity on the same side, appearing as irregular transverse ridging or a dark narrow strip down one or both lateral borders of the nail.

The thickened free end of the erythematous proximal nail fold becomes rounded, retracted and loses the ability to form a cuticle. The disease tends to run a protracted course interrupted by subacute exacerbations due to secondary *Candida* and bacterial infection with the formation of a small abscess in the space formed between the proximal nail fold and the nail plate. *Candida* spp. and bacteria are frequently isolated from beneath the proximal nail fold in patients with chronic paronychia (Daniel *et al.* 1996).

Depending on the major aetiological factors involved, chronic paronychia can be classified into the following types (Tosti & Piraccini 1997):

1 Contact allergy (topical drug ingredients, rubber, etc.) (Tosti *et al.* 1991).

2 Food hypersensitivity (a variety of immediate contact dermatitis due to foods).

3 *Candida* hypersensitivity (a similar reaction to that suggested in some patients with recurrent vaginitis).

4 Irritative reaction (irritative chronic paronychia may subsequently acquire a secondary hypersensitivity and develop chronic food hypersensitivity paronychia and/or *Candida* hypersensitivity paronychia).

5 *Candida* paronychia. True *Candida* paronychia is uncommon in temperate climates except in patients with chronic mucocutaneous candidiasis and HIV infection. In this condition proximal nail fold inflammation is usually associated with proximal onycholysis or onychomycosis due to *Candida*, which can be isolated both from the proximal nail fold and clipping of the affected nail plate. In contrast to *Candida* infection, non-dermatophyte moulds such as *Fusarium* (Fig. 4.19e) may produce subacute paronychia accompanied by proximal white onychomycosis especially in immunocompromised individuals (Baran *et al.* 1997). In *Fusarium* infection subsequent disseminated spread of the organism to affect other sites in the severely neutropenic patients may be preceded by a type of cellulitis proceeding from the nail fold (Rabodonirina *et al.* 1994).

Fig. 4.19 (*cont'd*) (d) Chronic paronychia with total dystrophic onychomycosis. (e) Chronic leuconychia with paronychia due to *Fusarium* infection. (f) Transverse green stripe due to *Pseudomonas* infection corresponding to exacerbation of the paronychia.

Scopulariopsis brevicaulis may be responsible for identical features with a white or yellow discoloration of the nail plate (Tosti *et al.* 1996a). Proximal subungual onychomycosis (PSO) may also be associated with marked periungual inflammation and black discoloration of the lunula region due to *Aspergillus niger* (Tosti & Piraccini 1998).

On rare occasions other infections may involve the nail fold causing a form of paronychia. Amongst the fungi, the agents of sporotrichosis and, less commonly, chromoblastomycosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and mycetoma may involve this area.

6 Bacterial paronychia. Bacteria may play a role in the pathogenesis of paronychia associated with *Candida* (see above). In addition, *Staphylococcus aureus* may cause an acute paronychia in an otherwise healthy patient. This generally arises as a result of an acute nail fold infection or whitlow and the nail fold may become swollen with subsequent discharge of pus via this area. Alternatively chronic paronychia caused by *S. aureus* is not infrequently seen in patients with skin disease, such as psoriasis or eczema, affecting the nail fold. Generally these are difficult to distinguish clinically from *Candida* infections. *Pseudomonas* infection of the proximal nail fold may produce transverse green stripes on the nail corresponding to exacerbations of the paronychia (Shellow & Koplon 1968) (Fig. 4.19f).

7 Paronychia caused by foreign bodies (Stone *et al.* 1964, 1975).

Total dystrophic onychomycosis (Figs 4.20–4.26)

Total dystrophic onychomycosis (TDO) represents the most advanced form of all the four previous types described above, especially DLSO. The nail crumbles and disappears leaving a thickened and abnormal nail bed which usually retains fragments of nail plate. All 20 nails may be involved in chronic generalized dermatophytosis (Hadida *et al.* 1966; Boudghène-Stambouli & Mérad-Boudia 1998). In the new form of total nail dystrophy observed in patients with AIDS, infection appears to have spread from under the proximal nail fold (PSO) but this has not been established in all cases. The dorsum of the nail plate may also be involved. The term acute TDO might be appropriate for this type of infection. In contrast to secondary TDO, primary TDO is observed only in patients suffering from chronic mucocutaneous candidiasis (CMC) or in other immunodeficiency states (Table 4.4) (Coleman & Hay 1997). *Candida* invasion rapidly involves all the tissues of the nail apparatus. The thickening of the soft tissues results in a swollen distal phalanx more bulbous than clubbed. The nail plate is thickened, opaque and yellow-brown in colour. Hyperkeratotic areas secondary to *Candida* invasion may develop in skin adjacent to the nail. Oral candidiasis is generally present in these patients. This syndrome, which usually occurs in childhood or infancy, recurs despite treatment. Dual or sole infection with dermatophytes may occur in patients with CMC.

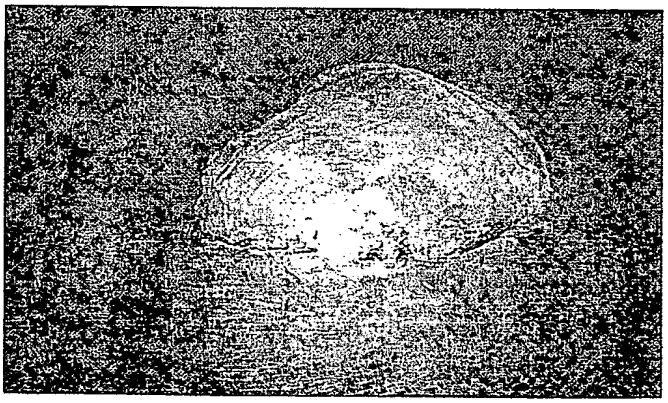


Fig. 4.20 Total dystrophic onychomycosis due to *Scopulariopsis brevicaulis*.

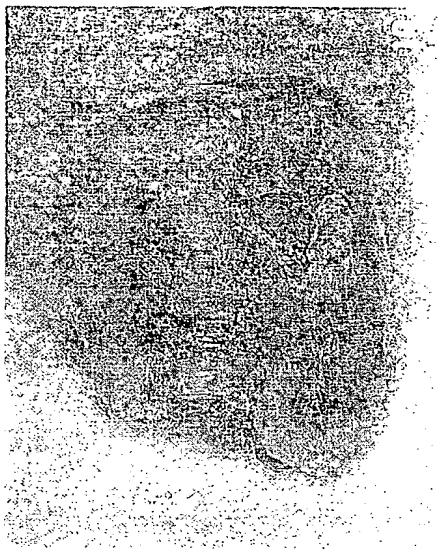


Fig. 4.21 Total dystrophic onychomycosis due to *Trichophyton rubrum*.

Fig. 4.22 Total dystrophic onychomycosis due to *Trichophyton rubrum*. (Courtesy of S. Goettmann-Bonvalot, France.)